Clinical Medicine

Plague Meningitis—A Retrospective Analysis of Cases Reported in the United States, 1970-1979

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Meningitis caused by Yersinia pestis *developed in 6 (6%) of a total of 105 patients with plague reported to the Centers for Disease Control from 1970 to 1979. Five of the six cases occurred in children aged 10 to 15 years. All six patients received antibiotic therapy before meningitis developed, which appeared between the 9th and 14th days after the onset of acute illness in five of the six patients. There were no neurologic sequelae. The antigenic and biochemical profiles of the* Y pestis *strains isolated from cerebrospinal fluid in the meningitis cases did not differ from those of the* Y pestis *strains obtained from blood and bubo aspirates in the other 99 patients, and neither did in vitro studies suggest antibiotic resistance. While plague meningitis is an uncommon complication of acute plague infection, physicians in the western United States should be aware that it may develop as much as 14 days after antibiotic therapy for the acute plague infection has been initiated.*

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While plague meningitis is an uncommon complication of human plague infections, its development is a possibility that treating physicians cannot afford to overlook. Of 105 cases of plague reported to the Centers for Disease Control (CDC) over a period of ten years—1970 to 1979—six of the patients had plague meningitis. We studied those 6 cases, comparing their case histories with those of the other 99 cases in which meningitis did not develop in an attempt to find any indication in the physical signs or symptoms or in the antibiotic therapy that might suggest a predisposition to the development of plague meningitis. We examined antimicrobial sensitivity of *Yersinia pestis* organisms, antigenic and biochemical characteristics of the organisms identified in cerebrospinal fluid (CSF) and the epidemiologic characteristics of all the 105 plague cases. We include in this report the case histories, physical findings and antibiotic therapy of the six cases in which plague meningitis did develop.

Patients and Methods

All human plague cases in this report were investigated by state and local health departments and the Indian Health Service in cooperation with the Plague Branch, Division of Vector-Borne Viral Diseases, Centers for Disease Control.

Case Definition and Study Population

We defined a case of plague as an illness reported to the CDC, occurring either in a person from whom *Y pestis* organisms were isolated or in one who showed a fourfold change in antibody titer (rise or fall) to *Y pestis.*

We defined a case of plague meningitis as an illness occurring in a patient from whom *Y pestis* was identified in the cerebrospinal fluid, or who had another form of documented plague infection, and a CSF Gram's stain showed either a bipolar, gram-negative rod or a positive fluorescent antibody test.

Laboratory Methods

We examined all bacteria by Wayson's stain and tested for growth characteristics in broth and agar, for mouse pathogenicity and for the production of F1 antigen in the fluorescent antibody test. We also tested all bacterial strains at 22°C and 37°C against a conditionally plague-specific phage in parallel with *Y pestis* strain 195/P and *Yersinia pseudotuberculosis* strain 1. The bacteria lysed by phage at both temperatures were considered *Y pestis.* We examined serologic specimens by the passive hemagglutination test for antibodies to *Y pestis.*[1] The Plague Branch laboratory confirmed all bacterial organisms and serologic tests.

We tested antimicrobial sensitivities of 4 CSF organisms, 2 bubo organisms from patients with meningitis and 94 other *Y pestis* organisms identified from patients without plague meningitis. For these sensitivity tests, we used microdilution minimal inhibitory concentration (MIC) test panels (Micro-Media Systems, Inc, Potomac, Md). The test panels included the following antibiotics: tetracycline, gentamicin, tobramycin, chloramphenicol, cephalothin, trimethoprim, amikacin, moxalactam, ampicillin, cefoxitin, cefamandole, rifampin, carbenicillin, penicillin, streptomycin, erythro-

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ABBREVIATIONS USED IN TEXT

CDC = Centers for Disease Control
CSF = cerebrospinal fluid
MBC = minimum bactericidal concentration
MIC = minimal inhibitory concentration

mycin, methicillin and sulfamethoxazole. The lowest concentration of antibiotic that resulted in no turbidity after 48 hours of incubation at 37°C was considered the MIC for a particular antibiotic. The minimum bactericidal concentration (MBC) was the minimal concentration of antibiotic that resulted in no growth of the organism when plated on trypticase soy agar and incubated at 37°C for 48 hours. We determined the MBC by plating onto trypticase soy agar plates with a calibrated loop (0.01 ml) the contents of the MIC dilution and the dilutions twofold and fourfold higher than the MIC dilution.

For biochemical characterization of strains of *Y pestis*, we used the API 20E System (Analytab Products, Plainview, NY). The dehydrated media contained in the microtubes were inoculated with suspensions of *Y pestis* (ten colonies, 48 hours old, suspended in 5 ml 0.85% sterile saline solution). We used the following in vitro tests for virulence markers of the *Y pestis* strains: the presence or absence of fraction I, V and W antigens; the presence or absence of the bacteriocin pesticin 2, and pigmentation on Congo red agar.[2]

For calculating relative risk estimates, we used standard Statistical Analysis System software packages.[3]

Results

Epidemiologic and Clinical Features

Of the 105 cases of plague infection reported to the CDC, plague meningitis developed in 6. Characteristics of patients in whom plague meningitis developed were similar to those of the other plague patients in respect to the sex ratio, geographic distribution and route of infection (Table 1), and the medical records did not indicate any early signs or symptoms in those patients in whom plague meningitis later developed compared with those patients whose clinical course did not include this complication. Five of the six cases were acquired in the summer months, and five occurred in children aged 10 to 15 years; the remaining case occurred in a 35-year-old woman.

TABLE 1.—*Characteristics of 105 Plague Patients, 1970-1979*

Patient Characteristics	Patients With Plague Meningitis	Patients With Other Types of Plague
Cases, No. (% of total)	6 (6)	99 (94)
Mean age (range), yr	17 (10-35)	24 (6 d-79)
Males, No. (%)	2 (33)	47 (47)
Females, No. (%)	4 (67)	52 (53)
Race, No. (%)		
Native American	1 (17)	27 (27)
White/other	5 (83)	72 (73)
Clinical features, No. (%)		
Buboes	3 (50)	81 (82)
Upper torso*	2 (33)	22 (22)
Lower torso†	1 (17)	59 (60)
None	3 (50)	18 (18)
Pneumonia	1 (17)	18 (18)
Osteomyelitis	1 (17)	0 (0)
Presumed mode of infection, No. (%)		
Flea bite	5 (83)	66 (67)
Direct tissue contact	1 (17)	18 (18)
Undetermined	0 (0)	15 (15)
State in which infection was acquired, No. (%)		
New Mexico	5 (83)	79 (80)
Arizona	1 (17)	16 (16)
All other	0 (0)	4 (4)

*Refers to cervical or axillary nodes.
†Refers to femoral or inguinal nodes.

Clinical signs and symptoms of meningitis developed between the 9th and 14th days after the initial onset of illness in five of the six patients, and all five had received some form of antibiotic therapy before its development. The sixth patient's condition on presenting for treatment casts doubt on the number of days of illness reported (see case 1). Blood cultures were positive for *Y pestis* in three patients. One of the six patients had a pneumonic infiltrate suggestive of plague pneumonia. No neurologic sequelae were observed, though the death of one patient limited follow-up to five patients. None of the case histories of the patients with meningitis indicated prior head trauma, a neurosurgical procedure, an ear-nose-throat operation or lumbar punctures before the development of plague meningitis.

Upper torso (cervical or axillary) buboes were clinically apparent in two of the six meningitis cases (33%) and in 22 of the 99 patients without meningitis (22%). The relative risk of meningitis developing with the presence of cervical or axillary nodes was 1.7 (95% confidence interval, 0.3 to 8.6). Three of the meningitis cases (50%), and 18 (18%) of the plague patients in whom meningitis did not develop had septicemic plague; the relative risk of meningitis developing among septicemic cases was 4.0 (95% confidence interval, 0.9 to 18.4).

Strain Characteristics

The Centers for Disease Control received organisms isolated from CSF from four of the cases of plague meningitis. The CSF organisms showed antimicrobial susceptibility patterns similar to those from patients with nonmeningitic plague. MIC and MBC data were not different for meningitic and nonmeningitic strains within and between groups for each antibiotic tested. Antigenic profiles, API profiles, pigmentation and bacteriocin production were also identical in meningitic and nonmeningitic organisms. In one case (case 3), the bacterial strains isolated from the CSF were compared with those from the bubo aspirates; they were identical in all characteristics.

Reports of Cases

CASE 1. In June 1974, a 13-year-old Navajo girl from New Mexico presented as an outpatient at a local hospital with headache, dizziness, fever, vomiting and general malaise. She was given penicillin G benzathine intramuscularly and sent home with no diagnosis. Two days later she was admitted to hospital with complaints of abdominal pain, continued fever and headache. On physical examination she was lethargic and dehydrated, with insect bites on the lower extremities. A lumbar puncture was done. Two hours after admission, before all admission laboratory reports were available, the patient became hypotensive, had a cardiac arrest and died.

CSF and blood cultures were later found positive for *Y pestis*. An autopsy showed generalized petechiae, enlarged mesenteric nodes and hemorrhagic lymph nodes in the left femoral region. There was evidence of toxic myocarditis,

hemorrhagic pericardial effusion and edematous lungs. The spinal cord, meninges and brain were not studied at postmortem examination. Probable source of infection: plague-positive fleas from rodent harborage near the patient's home.

CASE 2. In February 1975, an 11-year-old boy from Albuquerque was admitted to hospital with a temperature of 38.3°C (101°F); a painful, firm, 10-cm mass in the right axilla; a laceration on the right forearm, and a partially evulsed fingernail on the right middle digit. A regimen of methicillin sodium and streptomycin was started for cellulitis and an axillary abscess. Blood and lymph node aspirate yielded positive cultures for *Y pestis,* and the patient's therapy was changed on the eighth day of illness to tetracycline. His condition improved and he was discharged to home, but was readmitted on the 11th day of illness with lethargy and a stiff neck. A lumbar puncture was done, and CSF cultures were found positive for *Y pestis.* The patient was treated with a course of chloramphenicol and recovered without sequelae.

Source of infection: a confirmed plague-positive dead coyote that the patient found and skinned three days before his illness.[4] Probable route of infection: direct inoculation of *Y pestis* from the coyote tissues via open lesions on the patient's right forearm and middle finger.

CASE 3. In July 1975, a 15-year-old boy from Pecos, New Mexico, had the sudden onset of fever, malaise and diaphoresis; he was seen by a physician who prescribed a course of tetracycline for an undiagnosed illness. Nine days after the onset of illness, a severe, bitemporal headache developed, and the patient was admitted to hospital with a presumptive diagnosis of *Hemophilus influenzae* meningitis. After four days of ampicillin therapy given intravenously, the patient was afebrile, felt well and was discharged to home on a regimen of tetracycline. *Y pestis* was subsequently grown from the CSF. Probable source of infection: flea bites by plague-infected fleas, probably from one of the family dogs.

CASE 4. In July 1978, a 10-year-old girl from Otero County, New Mexico, presented to a local emergency department with fever, chills, abdominal cramps, headache and neck pain. On physical examination no focus of infection was found. A course of oral penicillin was started and the patient was sent home with no diagnosis. She remained febrile, cervical lymphadenopathy developed and she had persistent neck pain. On the sixth day of illness she was admitted to hospital and treatment was changed to administration of cephalexin. A lumbar puncture was done and culture was positive for *Y pestis* on the ninth day of illness. The patient was given chloramphenicol intravenously and ampicillin, and her condition improved within two days, though a pulmonary infiltrate developed and she had clinical evidence of calcaneal osteomyelitis early in her hospital stay. Therapy was continued in the hospital for three weeks to ensure adequate treatment of the patient's osteomyelitis. On the 25th day after the initial onset of illness, the patient was discharged to home on a regimen of oral tetracycline. Recovery was uncomplicated, with no neurologic or pulmonary sequelae. Probable source of infection: a kitten that had become ill with ocular exudate and had been handled by the patient.

CASE 5. In August 1978, a 35-year-old woman from Bernalillo County, New Mexico, reported having had two days of chills, myalgias and fever. She saw a local physician who was unable to provide a specific diagnosis. The next day, culture of a blood specimen from the patient's 3-year-old daughter, who had been ill several days before the onset of her mother's illness, was positive for *Y pestis.* The patient was admitted to hospital and treated with a course of tetracycline for presumptive plague. After four days she was discharged to home receiving oral tetracycline.

Two days after completing a six-day course of tetracycline and 12 days after the initial onset of illness, fever and headache developed and the patient was readmitted with a diagnosis of presumptive plague meningitis. A Gram's stain of the CSF showed gram-negative, bipolar-staining rods. The patient was given chloramphenicol intravenously and recovered without sequelae. Probable source of infection for both this patient and her daughter: infected fleas brought to the home by pet dogs.

CASE 6. In May 1979, a 13-year-old girl from Yavapai County, Arizona, was admitted to hospital with left lower quadrant tenderness and a subcutaneous abscess of the upper left anterior thigh. The initial clinical impression was pelvic inflammatory disease and an abscess of the left anterior thigh. After ten days of a regimen of penicillin given intravenously, erythromycin and cephalosporins, a severe headache and stiff neck developed, and she had a temperature of 38.9°C (102°F). On the 14th day of illness, a CSF culture grew both *Salmonella* species and *Y pestis.* The patient was then treated with a regimen of intravenous ampicillin and chloramphenicol; she made a gradual recovery and was discharged to home with no neurologic deficits. Probable source of infection: Investigation revealed rodent plague activity within 0.4 km (1/4 mi) of the patient's home. Infected fleas were probably brought into the patient's home by the family dogs.

Discussion

Y pestis infection most commonly occurs as the bubonic form of plague, which is simply an acute, usually regional, lymphadenitis. Prior reports have indicated that when plague meningitis occurs, it usually follows the bubonic infection.[5-7] The incidence of plague meningitis is low, ranging from 0.2% to 7.0% in published reports on plague infections in humans.[5,8,9]

The pathophysiology of plague meningitis is not well understood. Butler and co-workers have suggested that axillary or cervical buboes may predispose to meningitis through more direct lymphatic connections to the meninges.[9] Our data also suggest an increased risk of the development of meningitis in patients with cervical or axillary buboes, though the association was not statistically significant. In addition, septicemic plague also may be a risk factor for the development of meningitis: this increased risk is probably a result of bacteremia that leads to colonization of the meninges with *Y pestis* (although in a recent study on septicemic plague, no septicemic plague occurred in patients with meningitis[10]). Others have suggested that the meninges may be more susceptible to infection from organisms already adapted to mammalian host systems, such as in direct blood transmission from infected hosts.[11] Our data, however, do not support this suggestion: 19 of the cases of plague infection resulted from direct contact with infected animal tissues, and in only one did meningitis subsequently develop (case 2).

The most likely explanation for the development of plague

meningitis, consistent with observations of other researchers,[12] is that ineffective antibiotic therapy for the acute stages of plague infection allows the development of meningitis later in the course of the illness. The combination of the type of drug used, the rapidity with which it is administered following the onset of illness and the length of time it is administered may well be the important factors in successful treatment.

The findings of this study tend to support this theory. In case 2, the patient received the recommended antibiotics for plague infection—streptomycin and tetracycline—as well as methicillin, before the development of meningitis. The streptomycin and methicillin were not administered until the third day after the onset of illness, however, and the tetracycline was not administered until the eighth day. This may have been too late to prevent the spread of infection to the meninges. The patient in case 3 received a course of tetracycline, a recommended antibiotic for plague therapy, on the second day of acute illness. The dosage of 250 mg every six hours, however, was probably inadequate for a 15-year-old boy weighing 75 kg (165 lb). It is also possible that the patient did not comply with his treatment regimen, as he was not initially admitted to hospital. Case 5 is similar to case 3 in the ineffectiveness of tetracycline to prevent the development of meningitis. A course of tetracycline was started on the second day of illness, when the patient's daughter was diagnosed as suffering from plague infection. The tetracycline was taken for a total of eight days, four of them supervised in hospital. While poor compliance with the prescribed regimen does not seem to be a factor in this case and appropriate therapy was begun early in the acute illness, it is possible that the duration of the treatment period with tetracycline was inadequate. Cases 1, 4 and 6 are more consistent with cases of plague meningitis that have been described in the literature in that the antibiotics used before the development of meningitis were not the antibiotics of choice for treating plague.

Although tetracycline or doxycycline was included in the treatment regimen of four of the meningitis cases in this study—cases 2, 3, 5 and 6—we cannot conclude that tetracycline therapy predisposes to meningitis, as numerous other patients were effectively treated with it alone or in combination with other antibiotics. Tetracycline, however, does not readily cross the blood-brain barrier, and it is possible that the level of antibiotic in the central nervous system is insufficient to inhibit infection. If the meninges are seeded in the early stages of acute infection, as has been suggested,[6,7] tetracycline would have little effect. For the same reason, streptomycin therapy would also be ineffective (case 2).

Our study of the meningitis and nonmeningitis plague cases did not disclose any indicators to warn of the impending development of meningitis. Such clinical signs as the degree of temperature elevation were similar in both groups, and antigenic and antibiotic profiles of *Y pestis* strains were identical in the meningitic and nonmeningitic strains. Our investigation is obviously limited by the small number of plague meningitis cases. As additional cases are diagnosed, further analyses may reveal clinical or laboratory correlates for the development of the meningitis as an acute plague complication. Unfortunately, many questions concerning the pathophysiology of plague meningitis will remain unanswered until more clinical data are collected or until a suitable animal model is developed to study it. Nevertheless, despite limited understanding of the development of this complication, greater clinician awareness of meningitis as a sequela to acute plague infection could prevent its occurrence.

The choice of an antibiotic known to be effective against *Y pestis* and its administration for an adequate period of time are critical in the treatment of plague infection. If meningitis develops, 50 mg per kg per day of intravenous chloramphenicol, given in four doses a day for ten days, provides adequate therapy. Clinicians should also schedule follow-up examinations soon after discharging plague patients from the hospital. Educating the patients to the risks of the development of meningitis would also be a wise precaution, encouraging them to follow their treatment regimen carefully and to report any early central nervous system signs or symptoms.

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